Journal of the American College of Cardiology Vol. 47, No. 11 Suppl B

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.04.013

Myocardial Ischemia and Infarction

John A. Ambrose, MD, FACC
Fresno, California

ANTITHROMBOTIC STRATEGIES

The international Reduction of Atherothrombosis for Continued Health (REACH) registry was an enormous undertaking, involving more than 68,000 stable patients with coronary artery disease (CAD), cerebral vascular disease, peripheral arterial disease, and/or multiple atherothrombotic risk factors (1). At baseline, most of the patients in this contemporary registry were on optimal therapy: 75% on lipid-lowering therapy, 73% on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, 79% on antiplatelet therapy, and nearly one-half were taking beta-blockers.

This large global registry gives us an idea of the natural history of these patients, whether they have disease or just numerous risk factors. The results were a little discouraging. One-year follow-up data, available in 92% of patients, indicated that cardiovascular (CV) death, myocardial infarction (MI), stroke, or hospitalization occurred in 12.9% of the REACH registry subjects. In patients with established disease, the overall incidence of these major events was 14.5%, whereas in those with risk factors only, the event rate was 5.4%. Hard events—death, MI, or stroke—occurred in 3.5% of the registry patients at one year, although the incidence of these hard events increased in patients with multiple sites of established disease. Bleeding rates were low and intervention rates were modestly elevated, although most of the interventions were performed in peripheral vessels. The investigators concluded that atherothrombosis should be addressed as a global disease and events need to be decreased; the high event rate was disconcerting given the good therapy most patients received, and this requires attention.

In various randomized trials, investigators have focused on antithrombotic approaches in both stable and unstable patients with CAD. In the Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, patients with established CV disease at baseline or at high risk for an adverse event because of multiple risk factors were randomized to low-dose aspirin alone versus aspirin plus clopidogrel 75 mg/day. There was no significant difference between these two groups on follow-up, but the addition of clopidogrel when there was evidence of established CV disease at baseline produced a 12% reduction in the primary efficacy end point (6.9% vs. 7.9%; $p = 0.046$) (2). Given the small amount of benefit seen, we clearly need to know the cost efficacy of this approach before we routinely prescribe clopidogrel to all patients with CV disease.

In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, researchers evaluated heparin plus glycoprotein (GP) IIb/IIIa inhibition versus bivalirudin with GP IIb/IIIa inhibition or bivalirudin alone in moderate- to high-risk acute coronary syndrome (ACS) patients undergoing an early invasive strategy. The trial involved 13,800 patients; 99% of the patients underwent angiography at a median of 20 h after hospital admission, 56% underwent percutaneous coronary intervention (PCI), and 11% underwent subsequent coronary artery bypass graft surgery (3). The primary end points included an ischemic composite end point (death, MI, or unplanned revascularization); a composite of net clinical benefit, which included the ischemic composite end point plus major bleeding; or major bleeding by itself; all were calculated at 30 days.

Statistical analysis was performed for noninferiority as well as for superiority, and these were both predefined. The results showed that the ischemic composite was similar between groups, but major bleeding was seen less in the bivalirudin alone group, including retroperitoneal bleeds, access site bleeds, a decrease in hemoglobin, and the need for transfusion. Bivalirudin plus a GP IIb/IIIa inhibitor was noninferior to the heparin arm. The net clinical benefit was superior in the bivalirudin alone group versus heparin plus GP IIb/IIIa inhibition, based solely on the lower bleeding rates with bivalirudin (Fig. 1). In conclusion, the investigators suggested that bivalirudin can be substituted for either heparin or enoxaparin in these moderate- to high-risk ACS patients undergoing an early invasive strategy with the use of GP IIb/IIIa inhibitors. However, compared with either heparin or enoxaparin with GP IIb/IIIa inhibition, bivalirudin alone has a greater net clinical benefit because of less bleeding.

Another study dealing with high-risk ACS patients was presented by Dr. Adnan Kastrati, for the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 2) trial (4). In this trial, patients with rest pain and either ST-segment changes or an elevated baseline troponin set to undergo PCI were all pretreated with clopidogrel 600 mg at least 2 h before intervention. They were then randomized to standard-dose abciximab versus placebo at the time of intervention. The primary efficacy end point was a composite of death, MI, or urgent revascularization within 30 days, and safety was assessed as Thrombolysis In Myocardial Infarction (TIMI) bleeding. In the 2,022 patients randomized, abciximab significantly reduced the end point from 11.9% to 8.9%. Clinical benefit was seen only in the group with a baseline

From the UCSF-Fresno, Fresno, California.

JACC Vol. 47, No. 11 Suppl D
June 6, 2006:D13–7

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ACS	= acute coronary syndrome
ACUITY	= Acute Catheterization and Urgent Intervention Triage Strategy
CAD	= coronary artery disease
CHARISMA	= Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance
CV	= cardiovascular
ECG	= electrocardiogram
GFR	= glomerular filtration rate
GP	= glycoprotein
ExTRACT	= Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment
ISAR-REACT	= Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
LDL	= low-density lipoprotein
MI	= myocardial infarction
NCEP	= National Cholesterol Education Program
OASIS	= Organization to Assess Strategies for Ischemic Syndromes
PEACE	= Prevention of Events with Angiotensin-Converting Enzyme Inhibition
PCI	= percutaneous coronary intervention
PTCA	= percutaneous transluminal coronary angioplasty
REACH	= Reduction of Atherothrombosis for Continued Health
STEMI	= ST-segment elevation myocardial infarction
TIMI	= Thrombolysis In Myocardial Infarction

elevated troponin level, and in this group, there was an absolute 5.5% reduction with the use of abciximab. Of some surprise was the fact that there was no increase in bleeding with abciximab.

Dr. Salim Yusuf presented the Organization to Assess Strategies for Ischemic Syndromes-6 (OASIS-6) trial, which involved 12,092 ST-segment elevation myocardial infarction (STEMI) patients treated with either thrombolytic therapy or PCI within 12 h of symptom onset (5). It was a randomized double-blind comparison of fondaparinux 2.5 mg daily versus standard-dose unfractionated heparin in patients for whom heparin was indicated; or, for those patients with a contraindication to unfractionated heparin, the comparison was between fondaparinux 2.5 mg daily versus placebo. The heparin was given for two days, the fondaparinux for nine days.

The primary efficacy end point was death or re-infarction at 30 days, and the safety end point was severe bleeding. Primary PCI was performed in 31% of patients, with lytic therapy used in 45%, and no reperfusion therapy at all in 23% of patients. At 30-day follow-up, fondaparinux reduced the incidence of death or re-infarction (9.7% vs. 11.2%; $p = 0.008$). Throughout the trial, there was a statistically significant decrease in mortality with fondaparinux. The benefit was only seen among patients undergoing thrombolytic therapy or no reperfusion; PCI patients showed no benefit. The OASIS-6 investigators reported a tendency for fewer severe bleeding events ($p = 0.13$) with fondaparinux and a significant reduction in cardiac tamponade ($p = 0.02$) in the fondaparinux group. They concluded that for STEMI patients not undergoing primary PCI, fondaparinux as used in this trial reduced mortality and re-infarction without increasing severe bleeding.

The STEMI patients also were the focus of the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction 25 (ExTRACT-TIMI 25) study, which involved 20,479 patients randomized <6 h after onset and treated with any fibrinolytic agent (6). Patients received either enoxaparin for 7 days, which was age-adjusted with a lower dose for patients >75 years old, or unfractionated heparin for at least 48 h. The primary efficacy end point was all-cause death or nonfatal re-infarction at 30 days; the safety end point was major bleeding as in the OASIS-6 trial.

At 30 days, death or MI was significantly reduced with enoxaparin treatment, as was death, MI, or urgent revascularization; nonfatal MIs also were reduced 33% with the study drug (Table 1). Major bleeds, however, increased from 1.4% to 2.1% with enoxaparin, although there was no increase in intracranial hemorrhages, which were found in about 0.7% of the patient population. Antman et al. (6) concluded that for STEMI patients, enoxaparin for 7 days was superior to unfractionated heparin for 48 h.

I agree very much with the conclusions; both STEMI studies suggest that long-term antithrombins may be needed with fibrinolytic therapy and not just for the usual one or two days of heparin therapy. However, there will likely be less impact from these trials in the U.S. and in

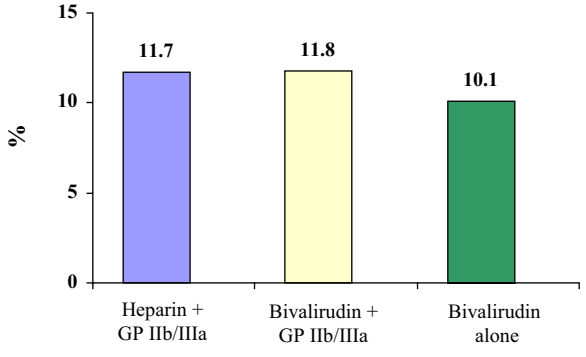

Figure 1. Acute Catheterization and Urgent Intervention Triage Strategy Trial (ACUITY): 30-day composite net clinical benefit (death, myocardial infarction, revascularization for ischemia, or major bleeding), showing superiority of bivalirudin alone versus heparin plus glycoprotein (GP) IIb/IIIa inhibitors ($p = 0.015$). Combination of bivalirudin and GP IIb/IIIa inhibitors was noninferior to heparin plus GP IIb/IIIa inhibitors.

Table 1. EXTRACT–TIMI-25: 30-Day Efficacy Outcomes

Outcomes	Enoxaparin (n = 10,256)	Unfractionated Heparin (n = 10,223)	p Value
Primary efficacy end point (death or nonfatal MI)	1,017 (9.9)	1,223 (12.0)	<0.001
Death	708 (6.9)	765 (7.5)	0.11
Nonfatal MI	309 (3.0)	458 (4.5)	<0.001
Urgent revascularization	213 (2.1)	286 (2.8)	<0.001
Death, nonfatal MI, or urgent revascularization	1,199 (11.7)	1,479 (14.5)	<0.001

Data are presented as n (%).
MI = myocardial infarction.

other countries where primary PCI or early post-MI angiography is the standard of therapy.

CAD AND RENAL DYSFUNCTION

Additional abstracts presented dealt with the prognosis or therapeutic options for patients with CAD and reduced renal function. The Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial evaluated the effect of ACE inhibition on mortality in 8,290 stable patients; this new analysis evaluated the effect of reduced renal function (7). Patients were randomized to trandolapril, up to 4 mg/day, or placebo, with a primary end point of death on follow-up. For the one-sixth of the population with reduced glomerular filtration rates (GFRs), defined as <60 mg/ml, there was a 27% reduction in mortality with trandolapril, although the overall trial showed no mortality advantage for the ACE inhibitor. Patients with low GFRs are often excluded from ACE inhibitor trials, but this study suggests that these are the patients most likely to benefit from ACE inhibition using trandolapril. Furthermore, this study and others presented at this meeting promote the concept that we should be routinely calculating creatinine clearances in our patients and not just simply relying on a serum creatinine level.

The TIMI study group looked at data from 13,140 non–ST-segment elevation ACS patients from five TIMI trials, assessing them for both diabetes and renal insufficiency, with the latter defined as none, mild, or moderate renal insufficiency based on GFR (8). After correlating the data to outcomes, renal insufficiency and diabetes were each associated with higher risk. We are more aware of diabetes-related risk, but in this study renal insufficiency alone produced more clinical events than did diabetes mellitus without renal insufficiency. Importantly, the two conditions acted synergistically to confer still higher risk. It seems that diabetes and renal insufficiency identify very high-risk patients who may require different therapies and procedures after ACS.

Prof. Keith Fox and his Edinburgh University team looked at the impact of renal dysfunction on the efficacy and safety of fondaparinux versus enoxaparin in the 20,078 non–ST-segment elevation ACS patients from the OASIS-5 trial (9). At nine days, mortality and bleeding rates increased with each quartile of creatinine, with mortality ranging from 0.97% in the lowest quartile to 3.12% in the highest (creatinine >1.2 mg/dl). Likewise, bleeding increased from 2.7% to 4.8% in the highest quartile, although hazard ratios for bleeding were consistently less with fondaparinux. Both six-month mortality and nine-day bleeding rates increased with the highest creatinine quartile for both antithrombin agents, but again these rates were consistently lower for fondaparinux versus enoxaparin. In the highest quartile, the six-month mortality rate was significantly lower with fondaparinux (9.5% vs. 11.4%; $p = 0.02$). The investigators concluded that rates of bleeding were influenced by baseline renal function with either antithrombin, and higher rates of mortality and bleeding associated with enoxaparin versus fondaparinux were most evident at the highest creatinine quartile. This suggests that enoxaparin may require more dose adjustments in the presence of renal dysfunction.

LIPID MANAGEMENT

An analysis of data from the National Health and Nutrition Examination Survey offers the encouraging news that more individuals seem to be managing their low-density lipoprotein (LDL) cholesterol. In analyzing data from 3,398 patients from the 1999 to 2000 data set compared with 3,746 from the 2001 to 2002 subset, researchers found that among high-risk patients, those with an LDL <100 mg/dl increased from 23% in the earlier period to 32% ($p < 0.01$) in the 2001 to 2002 subset (10). Considering just those high-risk patients with CAD, the percentage of patients with LDL levels <100 mg/dl increased from 27% to 41% ($p < 0.05$), which was much better than patients without heart disease, where there was only a trend toward better LDL management (20% to 26%; $p = 0.07$). Also encouraging is that the percentage of all high-risk patients with LDL ≥130 mg/dl who were untreated decreased (36% vs. 27%; $p < 0.01$); this time, the decrease was significant both in patients with CAD (25% vs. 16%; $p < 0.05$) and in those without CAD (44% vs. 33%; $p < 0.01$). This shows that we are making headway in treating high-risk patients, although there is still a long way to go to ensure adequate LDL lowering.

For an example of what we still need to work on, consider a sampling of 2004 data from 4,676 outpatients with CV disease; the data were extrapolated to the U.S. population to see how well LDL goals were being reached after the recommendations of the National Cholesterol Education

Program (NCEP) (11). The survey estimated that approximately 67.2 million people in the U.S. have risk factors for CAD or other CV disease, whereas another 35.1 million have CAD or CAD equivalent. In comparing LDL levels and statin use with NCEP targets for each group, approximately 60% of patients were receiving statin therapy, yet 48% still had LDL levels higher than NCEP III targets. Despite the fact that nearly half of treated patients were clearly not at their target level, only 7.1% were on high-dose statin therapy. So, even in the most recent data from 2004, LDL levels remain higher than NCEP goals in a substantial number of patients.

GENOMIC ASSOCIATION

Chen et al. (12) of the Cleveland Clinic looked at the genomic association of graft failure of the left internal thoracic artery-left anterior descending graft for myocardial revascularization in 230 patients. At 5 years, 30 patients had a stenotic or occluded graft; an additional 11 were stenotic or occluded at 10 years. The researchers analyzed 168 single-nucleotide polymorphisms from 150 vascular genes and found three single-nucleotide polymorphisms—F5, VTN, and MTP—that were significantly associated with graft failure ($p < 0.01$), whereas five others were associated with graft patency.

Several factors are thought to contribute to long-term graft patency: coagulation, cell proliferation, inflammation, and lipid metabolism. The mechanisms describing how these factors affect graft patency are presently unknown, but the work presented here may provide a glimpse into the future of medicine: using genetics to target both diagnosis and therapy.

STRATEGIES FOR DEALING WITH MYOCARDIAL INFARCTION

Various groups reported on strategies for treating MI patients; in Sweden, Björkland et al. (13) looked at a prospective cohort of consecutive STEMI patients who were ambulance-transferred to 66 different hospitals and treated with primary PCI between 2002 and 2004. The registry data were used to evaluate the relationship between a prehospital diagnostic strategy, which included a prehospital electrocardiogram (ECG), and outcome. A prehospital ECG was obtained in 911 patients and sent to the nearest hospital, where the patient received triage care. These patients were compared with a group of 1,106 with no prehospital ECG. Median time to therapy with the prehospital ECG was 55 min less ($p < 0.001$), and these patients tended to have a slightly lower 30-day mortality (2.4% vs. 3.6%, $p = 0.12$). Using multivariate analysis, use of a prehospital ECG was associated with a risk reduction of 47%, suggesting that a prehospital diagnostic strategy may be important, even when patients are triaged to primary PCI. Clearly, this is another example of the accepted adage that time is myocardium and anything that shortens the time to reperfusion has the potential to improve outcomes.

A study from France considered whether the volume of percutaneous transluminal coronary angioplasty (PTCA) influences the outcome of primary stenting or primary treatment for STEMI, even in the era of stenting. The Greater Paris PTCA registry included 37,848 procedures in 44 centers in 2001 and 2002; 87% of patients received stents (14). Morice et al. (14) correlated in-hospital mortality with the PTCA volume in both low- and high-risk patient subsets. High-risk patients were predefined as MI <24 h, cardiogenic shock, or out-of-hospital cardiac arrest.

High-risk patients had higher mortality rates in low-volume centers (<400 PTCAs annually; 8.54% vs. 6.75%; $p = 0.28$); mortality was the same for low-risk patients regardless of the volume of procedures performed at a center. Using multivariate analysis, predictors of death included age, female gender, annual volume, and high-risk procedures. Treatment at low-volume centers was also associated with a higher rate of complications. Thus, even in the era of widespread stenting, PTCA volume remains a factor in outcomes, and the investigators warned against promoting intervention in new hospitals with low numbers. Unfortunately, in this study no data were provided on individual physician statistics.

Another study followed up 500 patients treated with drug-eluting stents to determine the incidence and predictors of discontinuation of thienopyridine therapy one month after stenting for acute MI (15). Approximately 13.6% of the patients were no longer taking thienopyridines 30 days after drug-eluting stent placement. There were several univariate predictors of discontinuation (Table 2), but on multivariate analysis, only limited education was statistically significant. This is an important problem: in this particular study, mortality between 1 and 12 months was 7.5% in those who had stopped therapy versus 0.7% ($p < 0.001$) for those continuing therapy; hospitalizations were also higher with drug discontinuation (23% vs. 14%; $p = 0.08$). The results show that although discontinuation of therapy is a common problem, the ability to predict it happening is

Table 2. Univariate Predictors of Thienopyridine Therapy Discontinuation

Characteristic	Thienopyridine Therapy		p Value
	Discontinue	Continue	
Older age (yrs)	64	60	0.03
Completed high school	73%	89%	<0.001
Married	56%	71%	0.01
Avoid health care due to cost	24%	13%	0.02
Prior vascular disease	49%	30%	0.003
Lung disease	18%	8%	0.02
Anemia at presentation	19%	7%	0.001
Received discharge instructions about medication	88%	95%	0.05
Referred for cardiac rehabilitation	50%	64%	0.03

limited, and both better follow-up and a better solution for keeping patients from discontinuing therapy are needed.

PORCINE STEM CELLS

Finally, the transplantation of stem cells after MI is promising, but the literature is inconsistent, with some studies suggesting benefit and others indicating little or no clinical value. In a study from Tulane University, researchers studied the effect of adipose-derived stem cells, which are more prevalent than bone marrow-derived stem cells, in a porcine model (16). After occluding the left anterior descending artery for 3 h, investigators injected stem cells distally through the balloon catheter and then killed the animals 8 weeks later. Left ventricular wall thickness was significantly thicker in the infarct zone in those given the stem cells versus controls (5.9 mm vs. 3.6 mm) as well as in the border zone. Additionally, the treated pigs showed an increase in capillary density in the border zone ($p < 0.05$). Nuclear ejection fractions were 7% higher in the stem cell-treated pigs, and there was a lower end-diastolic volume. These data are promising and suggest a need for further studies to determine the role for adipose-derived stem cells to improve myocardial function after an MI; perhaps the effects are primarily attributable to reduced remodeling.

In summary, this meeting was full of new and significant randomized clinical trial data as well as interesting and important information in the abstracts. I extend my congratulations to all those involved.

Reprint requests and correspondence: Dr. John A. Ambrose, UCSF-Fresno, 445 South Cedar, Fresno, California 93702. E-mail: jamambrose@yahoo.com.

REFERENCES

1. Steg PG, Bhatt DL, Wilson PWF, et al., on behalf of the REACH Registry Investigators. Reduction of atherothrombosis for continued health (REACH) registry results: 1-year cardiovascular event rates in a global contemporary registry of over 68,000 outpatients with atherothrombosis (abstr). J Am Coll Cardiol 2006;47 Suppl A:168A.
2. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006 Mar 21 [epub ahead of print].
3. Stone GW, for the ACUITY Investigators. Prospective, randomized comparison of routine upfront initiation versus selective use of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes: the ACUITY Timing Trial. Presented at: ACC 55th Annual Scientific Session; Atlanta, GA: March 11–14, 2006.
4. Kastrati A, for the ISAR-REACT 2 Investigators. Prospective, randomized, double blind, placebo controlled trial of glycoprotein IIb/IIIa inhibition with abciximab in patients with acute coronary syndromes undergoing stenting after pretreatment with a high loading dose of clopidogrel. Presented at: ACC 55th Annual Scientific Session; Atlanta, GA: March 11–14, 2006.
5. Yusuf S, Mehta SR, Chrolavicius S, et al., OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA 2006;295:1519–30.
6. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med 2006;354:1477–88.
7. Solomon SD, Rice MM, Jablonski K, et al. Reduced renal function is associated with increased effectiveness of ACE inhibitor therapy in patients with chronic stable coronary disease in the prevention of events with ACE inhibition (PEACE) trial (abstr). J Am Coll Cardiol 2006;47 Suppl A:162A.
8. Ahmed S, Cannon CP, Giugliano RP, et al. The independent and combined risks of diabetes and non-endstage renal impairment in non ST-segment elevation acute coronary syndromes (abstr). J Am Coll Cardiol 2006;47 SupplA:207A.
9. Fox KAA, Bassand JP, Wallentin L, et al. The efficacy and safety of fondaparinux vs. enoxaparin in non-ST elevation ACS: impact of renal dysfunction (OASIS 5) (abstr). J Am Coll Cardiol 2006;47 Suppl A:195A.
10. Cullen MW, Gangnon RE, McBride PE, Stein JH, Keevil JG. National improvements in the recognition and treatment of patients at increased coronary risk: the National Health and Nutrition Examination Survey, 1999–2002 (abstr). J Am Coll Cardiol 2006;47 Suppl A:169A.
11. Steinberg BA, O'Hagen P, Chadwell P, Turner G, Cannon CP. Statin use and low-density cholesterol goals in 2004: how are we doing applying National Cholesterol Education Program III guidelines (abstr)? J Am Coll Cardiol 2006;47 Suppl A:209A.
12. Chen MS, Jia G, Luke MM, et al. Genomic association of graft failure of the left internal thoracic artery for myocardial revascularization (abstr). J Am Coll Cardiol 2006;47 Suppl A:165A.
13. Björkland E, Stenestrand U, Lindbäck J, et al. A prehospital diagnostic strategy reduces time to treatment and mortality in real life patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention (abstr). J Am Coll Cardiol 2006;74 Suppl A:192A.
14. Morice M-C, Spaulding C, Lancelin B, et al. Does hospital PTCA volume influence mortality and complication rates in the era of PTCA with systematic stenting? Results of the Greater Paris PTCA registry (abstr). J Am Coll Cardiol 2006;47 Suppl A:192A.
15. Spertus JA, Kettelkamp R, Vance C, et al. Incidence of, predictors of, and outcomes related to discontinuation of thienopyridine therapy at 1-month after coronary stenting in AMI (abstr). J Am Coll Cardiol 2006;47 Suppl A:236A.
16. Matthias N, Schwarzer M, Pinkernell K, Fotuhi P, Alt E. Effect of stem cells on left ventricle wall thickness and capillary density in pigs following myocardial infarction (abstr). J Am Coll Cardiol 2006;47 Suppl A:206A.